Supplementary Material S1

Description of the Studies used for analysis

IMPAACT P1110 was a Phase 1 study to evaluate the safety and PK of raltegravir oral granules for suspension given to neonates at risk of acquiring HIV-1 infection. The study was designed as an adaptive trial to determine a dosing regimen of raltegravir in the first 6 weeks of life. Mothers were followed until discharge from the labor and delivery unit, and neonates for 24 weeks after birth. Breastfeeding infants whose mothers were receiving raltegravir were excluded from enrollment. Initial raltegravir-unexposed and exposed groups of infants (Cohort 1) received 2 single raltegravir doses 1 week apart [1] and subsequent groups of infants (Cohort 2) received 6 weeks of a daily raltegravir dosing regimen selected by modeling incorporating data from the Cohort 1 infants [2]. All study infants received raltegravir in addition to standard of care ARV prophylaxis for prevention of perinatal transmission. An initial 6 raltegravir-unexposed Cohort 1 infants received single 3 mg/kg raltegravir doses within 48 hours of birth, with a second single 3 mg/kg dose administered between 7 and 10 days after birth (minimum of 12 PK evaluable neonates). Based on raltegravir concentration data from these infants, subsequent groups of 4 raltegravir-unexposed infants receiving initial 2 mg/kg doses and 6 raltegravir-exposed infants receiving initial doses of 1.5 mg/kg were enrolled. Plasma samples for raltegravir concentration assay were collected around the first dose (predose and 1-2, 4-8, 11-13 and 23-25 hours post dose), on Days 3 to 4 of life (single random sample) and around the 2nd dose (predose and 1-2 and 23-25 hours post dose). In Cohort 2, 26 raltegravir-unexposed infants were treated for 6 weeks with raltegravir 1.5 mg/kg QD from Days 1 to 7, 3 mg/kg BID from Days 8 to 28 and 6 mg/kg BID from Days 28 to 42. Plasma samples for raltegravir assay were collected around the first dose (pre-dose, 1-2 hours, 6-10 hours, and 20-24 hours post-dose), the second dose (3-6 hours post-

dose), Days 6 to 9 of life (pre-dose), Days 15 to 18 of life (pre-dose and 1-2 hours, 4-6 hours and 8-12 hours post-dose), Days 28 to 32 of life (pre-dose) and week 5 to 6 of life (pre-dose, 3-6 hours post-dose).

IMPAACT P1066 was a Phase 1 study to determine the appropriate treatment dose for raltegravir across postnatal age ranges of 4 weeks to 18 years of age. The starting raltegravir dose was 6 mg/kg granules for oral suspension every 12 hours. Two cohorts of children with HIV infection were included in this analysis: toddlers aged 6 months to < 2 years and infants aged 4 weeks to < 6 months. PK assessment included intensive (5-12 days after dosing) and sparse sampling (Weeks 4, 8, 12 and 24). Intensive PK samples were collected predose and 0.5, 1, 2, 4 and 12 hours after dosing in toddlers and predose and 0.5, 1, between 3 to 5 hours and between 8 to 10 hours after dosing in infants. Sparse PK samples were collected at following time points: 1 sample at 10 to 14 hours post-dose at Weeks 4 and 12, 2 samples (2 hours apart) at 0.5 to 6 hours post-dose at Week 8, and 2 samples (2 hours apart) at 6 to 12 hours post-dose at Week 24.

IMPAACT P1097 was a Phase 1 multicenter trial that evaluated the safety and exposure of raltegravir in infants who received no raltegravir dosing but were born to pregnant women with HIV-1 infection who received raltegravir during pregnancy [3, 4]. Maternal single plasma samples were collected within 48 hours of delivery. Infant blood samples to determine the washout elimination kinetics of raltegravir acquired across the placenta were collected at 1 to 5, 8 to 14, 18 to 24 and 30 to 36 hours after birth. Data from 19 mother-infant pairs were available.